PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A2933-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/BE2004/000124	International filing date *(day/month/year)* 27.08.2004	Priority date *(day/month/year)* 29.08.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/519, A61K31/5377, A61K31/541, A61K45/06, C07D475/04, C07D475/08, C07D475/00, A61P37/00, A61P37/02, A61P37/06, A61P9/00, A61P25/00, A61P35/00

Applicant
4 AZA BIOSCIENCE NV et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.06.2005	07.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Cielen, E Telephone No. +31 70 340-4540

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000124

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-69	as originally filed
Claims, Numbers	
1-12	filed with telefax on 08.11.2005
Drawings, Sheets	
1/7-7/7	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 13-27
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000124

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 8-12, with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 8-12, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000124

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☒ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☐ not complied with for the following reasons:
4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	7
	No:	Claims	1-6, 8-12
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I
Basis of the report

The amendments filed with the telefax dated 08.11.2005 are in accordance with Article 34(2)(b) PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV
Lack of unity of invention

For the claims as originally filed, a lack of unity objection within the meaning of Rule 13.1 PCT was raised, whereafter search fees were paid for inventions 1-3. **As the Applicant has now restricted the claims to invention 3 as originally filed, the requirements of Unity of Invention within the meaning of Rule 13.1 PCT are fulfilled, and the application will be prosecuted on the basis of invention 3 as originally defined.**

Re Item V:
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Present claims 8-12 involve compositions or substances in a method of treatment

of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D1: WO00/39129 A (WAER MARK JOSEPH ALBERT; HERDEWIJN PIET ANDRE MAURITS M (BE); LEUVEN) 6 July 2000 (2000-07-06)

D6: WO01/21619 A (PFLEIDERER WOLFGANG; KOTSONIS PETER (DE); SCHMIDT HARALD (DE); FROEHL) 29 March 2001 (2001-03-29)

V.iii. Article 33(2) PCT.

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12 is new in the sense of Article 33(2) PCT. None of the cited prior art documents discloses the compounds of present claim 1, pharmaceutical compositions containing them or their use for the treatment or prevention of ankylosing spondylitis, Sjogren's syndrome and allergic conditions.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of alternative medicines for the prevention or treatment of ankylosing spondylitis, Sjogren's syndrome and allergic conditions.

The proposed solution is the use of the compounds of present claim 1, optionally in combination with further immuno-suppressants and/or immunomodulator drugs, antihistamines and anti-allergic drugs.

(b) The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 1-6 and 8-12, as far as the treatment or prevention of allergic diseases is concerned, does not involve an inventive step in the sense of Article 33(3) PCT in the light of D1:

Document D1 discloses the use of pteridines for the treatment of allergic diseases (p. 1, line 1 - p. 2, line 10; p. 6, lines 6-12; p. 7, lines 26-34). Compounds 33-36 and 56 are 2-amino-4-morpholino-6-phenylpteridines, optionally substituted on the phenyl ring with Cl, p-OMe, 3,4-$(OMe)_2$ or 3,4-formylidene.

The compounds of the present application differ from the ones in D1 by the nature of the substituents present on the phenyl group; i.e. only one structural feature.

The problem to be solved by the present application can therefore be regarded as the provision of alternative 2-amino-4-morpholino-6-phenylpteridines for the treatment or prevention of allergic diseases.

The solution proposed in present claims 1-6 and 8-12 can at present not be considered as inventive because (1) the compounds of the present application appear obvious variants of the compounds of D1 without any documented unexpected and/or surprising effect and (2) it is not clear which non-obvious technical problem would have hindered the skilled person to synthesis compounds with the substitution pattern as claimed in present claim 1.

The dependent claims 2-5 and 9-12 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step.

(c) The subject-matter of present claims 1-12, as far as the treatment or prevention of ankylosing spondylitis, Sjogren's syndrome or asthma is concerned, may involve an inventive step for the following reasons:

1. Document D1 discloses the use of pteridines for the treatment of allergic diseases and auto-immune disorders, optionally in combination with further immunosuppressants (p. 1, line 1 - p. 2, line 10; p. 2, line 34 - p. 3, line 12; p. 4, lines 3-7; p. 6, lines 6-12; p. 7, lines 26-34; p. 17, line 30 - p. 18, line 13; p. 19, lines 8-20; p. 19, line 34 - p. 20, line 14; claims 1-8, 13-17). Compounds 33-36 and 56 are 2-amino-4-morpholino-6-phenylpteridines, optionally substituted on the phenyl ring with Cl, p-OMe, 3,4-$(OMe)_2$ or 3,4-formylidene.

Document D6 reports that disease states associated with a disturbed NO metabolism, such as auto-immune diseases, can be treated with pteridine derivatives (p. 1, lines 10-14; p. 4, lines 19-24; p. 5, line 1 - p. 7, line 10; p. 15, lines 11-30; p. 16, lines 13-14; claims 1-8). Compounds 27-30 are 2-amino-4-morpholino-6-phenylpteridines, optionally substituted on the phenyl ring with Cl, p-OMe or 3,4-$(OMe)_2$.

The compounds of the present application differ from the ones in D1 or D6 by the nature of the substituents present on the phenyl group; i.e. only one structural feature.

The problem to be solved by the present application can therefore be regarded as the provision of alternative 2-amino-4-morpholino-6-phenylpteridines for the treatment or prevention of the specific allergic disease asthma and the specific auto-immune diseases ankylosing spondylitis and Sjogren's syndrome.

The solution proposed in present claims 1-12, as far as the treatment or prevention of asthma, ankylosing spondylitis and Sjogren's syndrome is concerned, may be considered as inventive for the following reasons:

Not only would the skilled person have to modify the substituents on the phenyl group of the compounds of D1 and D6, he then would have to select the particular allergic and auto-immune diseases presently claimed, which were disclosed neither in D1 nor in D6.

2. Moreover, the presently disclosed data (Table 4, p. 69) demonstrate that several illustrative compounds of examples 72 to 102 (present claim 1) show a significant effect in inhibiting the production of TNF-α. Since the involvement of TNF-α in asthma, ankylosing spondylitis and Sjogren's syndrome was already known from the prior art (documents not shown), the use of the compounds of present claim 1 for the treatment or prevention of these diseases appears to involve an inventive step.

CLAIMS

1. A pteridine derivative selected from the group consisting of:

- 2-amino-4-morpholino-6-(4-acetanilide) pteridine,
- 2-amino-4-morpholino-6-(3-acetanilide) pteridine,
- 2-amino-4-morpholino-6-(4-aminophenyl) pteridine,
- 2-amino-4-morpholino-6-(3-aminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-benzoylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-phenoxyacetylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-propionylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-furoylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-cyclohexanoylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-[4-(4-chlorobenzoyl)aminophenyl] pteridine,
- 2-amino-4-morpholino-6-(4-benzyloxyacetylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(4-isonicotinoylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(4-naphtoylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(4-methylsulfonylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(4-ethylsuccinylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-[4-(4-methylbenzoate)aminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-benzoylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-benzensulfonylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(3-phenoxyacetylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-isonicotinoylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-cyclohexanoylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-[3-(4-methylbenzoate)aminophenyl] pteridine;
- 2-amino-4-morpholino-6-(3-ethylsuccinylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-ethylmalonylaminophenyl) pteridine;
- 2-amino-4-morpholino-6-(3-benzyloxyacetylaminophenyl) pteridine,
- 2-amino-4-morpholino-6-(3-ethylsulfonylaminophenyl)pteridine,
- 2-amino-4-morpholino-6-[3-Boc-(L)-phenylalanine-aminophenyl] pteridine;
- 2-amino-4-morpholino-6-[3-Boc-(D)-phenylalanine-aminophenyl] pteridine;
- 2-amino-4-morpholino-6-[3-Boc-(L)-tryptophane-aminophenyl] pteridine;
- 2-amino-4-morpholino-6-[3-Boc-(D)-tryptophane-aminophenyl] pteridine, and
- 2-amino-4-morpholino-6-(4-hydroxyphenyl) pteridine.

2. A pharmaceutical composition comprising as an active principle at least one pteridine derivative according to claim 1.

3. A pharmaceutical composition according to claim 2, further comprising one or more biologically active drugs selected from the group consisting of immuno-suppressant and/or immunomodulator drugs, antihistamines, and anti-allergic drugs.

4. A pharmaceutical composition according to claim 3, wherein said biologically active drug is an immunosuppressant drug selected from the group consisting of cyclosporin A; pentoxyfylline; daltroban, sirolimus, tacrolimus; rapamycin; leflunomide; mycophenolic acid and salts thereof; azathioprine, brequinar; gusperimus; 6-mercaptopurine; mizoribine; chloroquine; hydroxychloroquine; etanercept; infliximab; and kineret.

5. A pharmaceutical composition according to claim 3, wherein said biologically active drug is an immunomodulator drug selected from the group consisting of acemannan, amiprilose, bucillamine, ditiocarb sodium, imiquimod, Inosine Pranobex, interferon-β, interferon-γ, lentinan, levamisole, pidotimod, romurtide, platonin, procodazole, propagermanium, thymomodulin, thymopentin and ubenimex.

6. Use of a pteridine derivative according to claim 1 for the manufacture of a medicament for the prevention or treatment of a disease selected from the group consisting of ankylosing spondylitis, Sjogren's syndrome, and allergic conditions.

7. Use according to claim 6, wherein said allergic condition is asthma.

8. A method of prevention or treatment of a disease selected from the group consisting of ankylosing spondylitis, Sjogren's syndrome, and allergic conditions, comprising the administration to the patient of an effective amount of a pharmaceutical composition comprising as an active principle at least one pteridine derivative according to claim 1.

9. A method of prevention or treatment according to claim 8, wherein an effective amount of the pharmaceutical composition corresponds to an amount in the range from 0.01 mg to 20 mg of the pteridine derivative per day and per kg body weight of the patient.

10. A method of prevention or treatment according to claim 8 or claim 9, wherein said pharmaceutical composition further comprises one or more biologically-active drugs selected from the group consisting of immunosuppressant and/or immunomodulator drugs, antihistamines, and

anti-allergic drugs, or is administered in combination with an effective amount of a second pharmaceutical composition comprising one or more biologically-active drugs selected from the group consisting of immunosuppressant and/or immunomodulator drugs, antihistamines, and anti-allergic drugs.

11. A method of prevention or treatment according to claim 10, wherein said biologically active drug is an immunosuppressant drug selected from the group consisting of cyclosporin A; pentoxyfylline; daltroban, sirolimus, tacrolimus; rapamycin; leflunomide; mycophenolic acid and salts thereof; azathioprine, brequinar; gusperimus; 6-mercaptopurine; mizoribine; chloroquine and hydroxychloroquine.

12. A method of prevention or treatment according to claim 10, wherein said biologically active drug is an immunomodulator drug selected from the group consisting of acemannan, amiprilose, bucillamine, ditiocarb sodium, imiquimod, Inosine Pranobex, interferon-β, interferon-γ, lentinan, levamisole, pidotimod, romurtide, platonin, procodazole, propagermanium, thymomodulin, thymopentin and ubenimex.